REMARKS

The Office Action has been carefully reviewed. Reconsideration and allowance of the claims in light of the foregoing amendments is respectfully requested.

A petition and fee for a three-month extension of time is submitted separately. An information disclosure statement and fee also accompanies this response.

Claims 1-2 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention. Specifically, the Office Action stated that claim 1, line 11, recites the phrase "whereby a difference in the high resolution powder diffraction patterns of said first sample slurry and said second sample slurry provides a positive indication" which is vague and indefinite. It is unclear to the Office how much difference is necessary to become a positive indication. For example, if there is a minor difference caused by experimental variation or background noise, one skilled in the art would not conclude that this is a positive indication. Clarification of the metes and bounds of this phrase via clearer wording is requested. Claim 2 was also rejected due to its dependency upon claim 1. Further, claim 1 penultimate line, recites the phrase "said selected polycrystalline macromolecule material" which lacks clear antecedent basis. Two selected polycrystalline macromolecule materials are mentioned in lines 3-6. Because these materials can be interpreted to be two different types of polycrystalline macromolecule materials, it is unclear which one is being referred to in the penultimate line of the claim. Clarification of the metes and bounds of this phrase via clearer wording is requested. Claim 2 was also rejected due to its dependency upon claim 1.

Claim 1 has been amended to indicate that the second sample slurry of is of the same polycrystalline macromolecule material as the first sample slurry. This corrects and removes the objection based on lack of antecedent basis for the phrase "said selected polycrystalline macromolecule material" in the penultimate line. Claim 1 has also been amended to clarify the terms "difference in" and "provides a positive indication of" such that the claim recites that "whereby a change between the high resolution powder diffraction patterns of said first sample slurry and said second sample slurry indicates formation of a complex between said selected polycrystalline macromolecule material and at least one of said one or more ligands.

Claims 1-2 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Nienaber et al. (U.S. Patent No. 6,297,021) in view of Ahlem et al. (U.S. Patent No. 6,667,299). The Office Action stated that Nienaber et al. describe a process for screening of ligand binding to target biomolecules using X-ray crystallography via obtaining a crystal of the target biomolecule, exposing the crystal to one or more samples, and obtaining an X-ray diffraction pattern to determine whether a ligand/receptor complex was formed. Nienaber et al. describe comparing the exposed target biomolecule crystal (second sample) X-ray diffraction pattern with the X-ray diffraction pattern obtained from a non-exposed target biomolecule crystal (first sample) (claim 1) which represents diffraction patterns from the first and second samples, as stated in claim 1. Nienaber et al. describe exposing the target biomolecule by soaking in solution with one or more samples which represents the sample slurry of a selected crystalline macromolecule material, one or more ligands, and a solvent, as stated in claim 1. Nienaber et al. describe buffers and precipitant solutions may be used to stabilize mixtures and soak them into the crystal (col. 8, lines 6-8), which represent components of the first and second sample slurries mentioned above. Nienaber et al. describe Figure 3 where X-ray diffraction dataset is collected (col. 2, lines 33-37). Nienaber et al. describe crystallographic data are collected and processed where each reflection (spot) on the diffraction pattern is assigned an index and intensity (col. 8, lines 35-38). Nienaber et al. describe converting the diffraction data to electron density maps of 3-D pictures of ligands and biomolecules (from second sample slurry) or biomolecules alone (from first sample slurry) (col. 8, lines 45-49). Nienaber et al. describe Fo-Fc maps that are subtractions of the native protein (first sample) from crystals soaked in library ligand mixture (second sample), which results in positive and negative peaks (col. 8, lines 50-56). Nienaber et al. describe positive peaks represent ligand binding to the target biomolecule (col. 8, lines 58-61). Nienaber et al. describe comparing maps of exposed crystals with unexposed crystals to differentiate positive indications densities found in Fo-Fc maps (col. 9, lines 7-11), which represents positive indications of ligand-biomolecule complexes. Nienaber et al. describe comparing the structure of the original crystal (without ligands) with the exposed crystal structure (exposed to ligands) (col. 6, lines 50-57), which represent comparing the first and

second sample slurry. Nienaber et al. describe using a method (CrystaLEAD™) as well as multiple detectors or a single synchrotron beamline which facilitates true high-throughput screening (col. 6, lines 40-49 and col. 24, lines 60-66). Nienaber et al. describe collecting high resolution data (col. 9, lines 45-46; col. 14, lines 30-32; and col. 15, lines 40-43). Nienaber et al. describe biomolecules, such as proteins (col. 1, lines 20-22) as stated in instant claim 2. Nienaber et al. do not describe polycrystalline macromolecule material or using powder diffraction data.

Ahlem et al. describe using power X-ray diffraction (XRD) methods that have been used to characterize various crystalline compounds (col. 24, lines 17-18). Ahlem et al. state the diffraction pattern, or portions thereof, obtained from a crystalline compound, is usually diagnostic for a given crystal form, although weak or very weak diffraction peaks may not always appear in replicate diffraction patterns obtained from successive batches of crystals (col. 24, lines 22-27). Peaks on XRD spectra are usually suitable to characterize or describe a crystalline material such as BrEA hemihydrate from other crystal forms that contain the same compound (col. 24, lines 31-38). Ahlem et al. describe also doing single crystal X-ray crystallography on BrEA hemihydrate (col. 25, lines 59-60). The Office Action noted that Paul Heiney on a webpage called "What is X-ray diffraction (XRD)" mentions that powder diffraction uses samples consisting of many small crystallites (page 4), which represents polycrystalline material. This reference is not being used as prior art, but merely to further define the powder X-ray diffraction sample used by Ahlem et al.

Nienaber et al. state that CrystaLEAD™ provides an efficient screening method for identifying compounds that will bind to a target biomolecule (col. 3, lines 9-11). Nienaber et al. state that this process had not been used before because the method was too complicated, time consuming, and problems obtaining crystals (col. 3, lines 26-38). However, Nienaber et al. state that currently available technology has overcome many of these perceived barriers (col. 3, lines 39-40). Nienaber et al. state various time saving, practical, and feasible improvements to the methodology (col. 3, lines 50-64). It would have been obvious to the person of ordinary skill in the art at the time the invention was made to improve any barriers of screening ligands via crystallography, as stated by Nienaber et al. such as using various crystallographic techniques as

described by Ahlem et al. Therefore, one of ordinary skill in the art would have been motivated to screen ligands (as stated by Nienaber et al.) that will bind to polycrystalline biomolecule material via powder diffraction data techniques (as stated by Ahlem et al.) as this would provide time saving procedures in high throughput screening (as stated by Nienaber et al.). One of skill in the art would have been motivated to make these modifications as single X-ray crystallography and powder crystal x-ray diffraction are two known ways of obtaining crystals, as described by Ahlem et al. Thus, the Office Action concluded that Nienaber et al. in view of Ahlem et al. motivate the limitations in claims 1 and 2.

Applicants submit that Nienaber et al. describe a process for screening of ligand binding to target biomolecules using X-ray crystallography. Such a process requires a crystal and that has been one of the existing problems in studying the ligand molecule interactions of many macromolecules such as proteins. As noted by the Office Action, Nienaber et al. do not describe polycrystalline macromolecule material or using powder diffraction data. While Ahlem et al. mention both powder x-ray diffraction and single x-ray crystallography, there is no suggestion by Ahlem et al. that powder x-ray diffraction can be used to study the binding of ligands to macromolecules. Rather, Ahlem et al. simply state that the peaks on powder XRD spectra combined with one or more other diagnostic data such as melting point or the like is usually suitable to characterize or describe a crystalline material such as BrEA hemihydrate from other crystal forms that contain the same compound. As Ahlem et al. describe various forms of BrEA hemihydrate at column 24, line 53 to column 25, line34, it is submitted that Ahlem et al. seek to differentiate their preferred form of BrEA hemihydrate from other forms of BrEA hemihydrate via powder diffraction data. That Ahlem et al. mention both powder x-ray diffraction and single x-ray crystallography is no hint to one seeking to study high throughput screening of binding of ligands to macromolecules that high resolution x-ray powder diffraction can be used in place of the standard x-ray crystallography as used by Nienaber et al. Neither Nienaber et al. nor Ahlem et al. contemplate producing slurries of a polycrystalline macromolecule. Neither Nienaber et al. nor Ahlem et al. contemplate producing slurries of a polycrystalline macromolecule in the presence of one or more ligands. Finally, neither Nienaber et al. nor Ahlem et al. contemplate

comparing high resolution powder diffraction patterns of two slurry mixtures (each containing the same polycrystalline macromolecule) in order to find indications of formation of a complex between a ligand and the polycrystalline macromolecule. In view of these differences, applicants submit that claims 1-2 are not obvious under 35 U.S.C. 103(a) over Nienaber et al. in view of Ahlem et al.

In view of the foregoing amendment and remarks, claims 1-2 are urged to be allowable over 35 U.S.C. 103 and 112. If the Examiner believes there are any unresolved issues despite this amendment, the Examiner is urged to contact the applicants' attorney undersigned below for a telephonic interview to resolve any such issue. A favorable action is solicited.

Respectfully submitted,

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